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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: FORM V CRYSTALLINE [R-(R*,R*)]-2-(4-FLUOROPHENYL)-8,8G(D)-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1- HEPTANOIC ACID HEMI CALCIUM SALT. (ATORVASTATIN)

(57) Abstract: A novel crystalline form of [R-(R*,R*)]-2-(4-fluorophenyl)-8,8-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt designated as Form V is characterized by its X-ray powder diffraction and/or solid state NMR is described, as well as methods for the preparation which is useful as an agent for treating hyperlipidemia and hypercholesterolemia.

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Form V crystalline [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt. (ATORVASTATIN)

5 **FIELD OF THE INVENTION**

The present invention relates to a process for the production of form V of [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (ATORVASTATIN). The present invention further relates to a
10 method of production of form V of [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt and its isolation. This novel crystalline form of atorvastatin is useful as a pharmaceutical agent, as an
15 inhibitor of the enzyme 3-hydroxy-3 methylglutaryl-coenzyme A reductase (HMG-CoA reductase) and is thus useful as a hypolipidemic and hypocholesterolemic agent.

BACKGROUND OF THE INVENTION

20 Atorvastatin calcium, a synthetic HMG-CoA reductase inhibitor, is used for the treatment of hyperlipidemia and hypercholesterolemia, both of which are risk factors for arteriosclerosis and coronary heart disease.

United States Patent Number 4,681,893, which is herein incorporated by reference, discloses certain intermediates used in the synthesis of
25 atorvastatin. United States Patent Number 5,273,995, which is herein incorporated by reference, discloses the enantiomer having the R form of the

ring-opened acid of [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid. United States Patent Numbers 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,397,792; and 5,342,952, which are herein incorporated by reference, disclose various processes and key intermediates for preparing atorvastatin.

Atorvastatin is prepared as its calcium salt, i.e., [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-

[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (2:1). The process by which atorvastatin is produced should be

- (i) easily scaled up for commercial production
- (ii) The product should be in a form that is readily filterable and easily dried.
- (iii) The product is stable for extended periods of time without the need for specialized storage conditions.

The processes in the above United States Patents disclose amorphous atorvastatin which has unsuitable filtration and drying characteristics for large-scale production and must be protected from heat, light, oxygen, and moisture.

To overcome the above disadvantages, the present invention provides atorvastatin in a new crystalline form designated Form V. Form V atorvastatin has different physical characteristics compared to the previous crystalline or amorphous product.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to crystalline Form V atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ , d-spacings, and relative intensities measured on a STOE/STADI-P X-ray powder diffractometer with germanium monochromated Cu K alpha 1(L =1.54056 Angstroms) Siemens D-500 diffractometer with CuK. Radiation:

| 2 θ -OBS | 2 θ -CALC | D-OBS | Relative Intensity(%) |
|-----------------|------------------|---------|-----------------------|
| 5.340 | 5.340 | 16.5350 | 7.9 |
| 8.618 | 8.611 | 10.2525 | 23.1 |
| 8.724 | 8.697 | 10.1282 | 25.2 |
| 8.950 | 8.946 | 9.8727 | 30.1 |
| 9.819 | 9.828 | 9.0004 | 28.7 |
| 10.094 | 10.063 | 8.7564 | 20.0 |
| 11.335 | 11.337 | 7.8004 | 21.0 |
| 16.673 | 16.671 | 5.3128 | 100.0 |
| 17.955 | 17.947 | 4.9363 | 19.3 |
| 19.161 | 19.132 | 4.6283 | 43.3 |
| 21.479 | 21.479 | 4.1338 | 69.2 |
| 22.561 | 22.568 | 3.9378 | 38.3 |
| 23.154 | 23.122 | 3.8384 | 43.2 |
| 23.576 | 23.588 | 3.7707 | 33.7 |
| 24.324 | 24.309 | 3.6563 | 6.6 |
| 24.560 | 24.559 | 3.6217 | 10.5 |

| | | | |
|--------|--------|--------|------|
| 26.268 | 26.295 | 3.3900 | 8.1 |
| 28.224 | 28.217 | 3.1593 | 9.8 |
| 28.804 | 28.781 | 3.0970 | 9.9 |
| 29.199 | 29.195 | 3.0560 | 21.7 |
| 30.370 | 30.371 | 2.9408 | 10.8 |
| 31.893 | 31.909 | 2.8037 | 12.3 |
| 37.356 | 37.337 | 2.4053 | 10.3 |

Further, the present invention is directed to crystalline Form V atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million measured on a Bruker DRX-500MHz spectrometer:

| Assignment (8kHz) | Chemical Shift |
|--------------------------------|----------------|
| Spinning Side Band | 59.64 |
| Spinning Side Band | 157.9 |
| Spinning Side Band | 161.59 |
| C12 or C25 | 183.4 |
| C12 or C25 | 177.6 |
| C16 | 166.4 |
| | 159.5 |
| Aromatic Carbons | 136.4 |
| C2-5, C13-C18, C19-24, C27-C32 | 134.4 |
| | 130.2 |
| | 128.8 |
| | 127.5 |
| | 122.7 |

| | |
|--------------------------------------|------------------------------|
| | 120.1 117.0 112.9 |
| C8, C10 | 72.3 69.5 67.3 64.0 |
| Methylene Carbons C6, C7, C9, C11 | 46.5 40.5 |
| C33 | 25.5 24.0 |
| C34 | 20.42 |

The present invention further relates to a process for the preparation of Form V atorvastatin Calcium and hydrates thereof which comprises

- (i) stirring heterogeneous mixture of atorvastatin calcium in a mixture of water and absolute ethanol;
- (ii) filtering to get the solid;
- (iii) drying to get Form V atorvastatin calcium.

The ratio of water and absolute alcohol is in the range of 3 :1 to 8:1, preferably 4.67 : 1.

Stirring is carried at 25 - 50 deg centigrade, preferably 40 deg centigrade.

The stirring is carried for 10 - 25 hrs, preferably 17 hours.

The final product is dried in vacuum tray drier.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS

The invention is further described by the following non-limiting examples which refer to the accompanying Figures 1 to 4, short particulars of which are given below.

Figure 1:

Diffraction pattern of heterogeneous mixture of atorvastatin calcium. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

Figure

Diffraction pattern of Form V atorvastatin. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

Figure 3:

The solid state ^{13}C nuclear magnetic resonance spectrum of heterogeneous mixture of atorvastatin calcium.

Figure 4:

The solid state ^{13}C nuclear magnetic resonance spectrum of Form V atorvastatin calcium.

DETAILED DESCRIPTION OF THE INVENTION

Crystalline Form V atorvastatin may be characterized by its X-ray powder diffraction pattern and/or by its solid state nuclear magnetic resonance spectra (NMR).

X-RAY POWDER DIFFRACTION - Form V Atorvastatin

Form V atorvastatin was characterized by its X-ray powder diffraction pattern. Thus, the X-ray diffraction pattern of Form V atorvastatin was

measured germanium monochromated Cu K alpha 1(L =1.54056 Angstroms)

Equipment

STOE/STADI-P powder diffractometer with an IBM-PC compatible interface , STOE software = DIFFRAC AT (SOCABIM 1986, 1992). CuK α radiation (20 mA, 40 kV, $k = 1.5406 \text{ \AA}$) slits I and II at 10) electronically filtered by the Kevex Psi Peltier Cooled Silicon [Si(Li)]Detector (Slits: III at 10 and IV at 0.150).

Methodology

The silicon standard is run each day to check the X-ray tube alignment. X-ray generator; sealed tube; 30KV; 5mA Curved PSD detector in the transmission mode, step size 0.03 degrees 2theta range 3-60 in two frames of 5 minutes exposure each per frame. Raw sample mounted on the transmission block on mylar (x-ray proof) film and rotated to avoid orientation effects. Table 1 lists the 2 θ , d-spacings, and relative intensities of all lines in the ungrounded sample with a relative intensity for crystalline Form V atorvastatin. It should also be noted that the computer-generated unrounded numbers are listed in this table.

TABLE 1. Intensities and Peak Locations of All Diffraction Lines With Relative Intensity for Form V Atorvastatin

| 2 θ -OBS | 2 θ -CALC | D-OBS | Relative Intensity(%) |
|-----------------|------------------|---------|-----------------------|
| 5.340 | 5.340 | 16.5350 | 7.9 |

| | | | |
|--------|--------|---------|-------|
| 8.618 | 8.611 | 10.2525 | 23.1 |
| 8.724 | 8.697 | 10.1282 | 25.2 |
| 8.950 | 8.946 | 9.8727 | 30.1 |
| 9.819 | 9.828 | 9.0004 | 28.7 |
| 10.094 | 10.063 | 8.7564 | 20.0 |
| 11.335 | 11.337 | 7.8004 | 21.0 |
| 16.673 | 16.671 | 5.3128 | 100.0 |
| 17.955 | 17.947 | 4.9363 | 19.3 |
| 19.161 | 19.132 | 4.6283 | 43.3 |
| 21.479 | 21.479 | 4.1338 | 69.2 |
| 22.561 | 22.568 | 3.9378 | 38.3 |
| 23.154 | 23.122 | 3.8384 | 43.2 |
| 23.576 | 23.588 | 3.7707 | 33.7 |
| 24.324 | 24.309 | 3.6563 | 6.6 |
| 24.560 | 24.559 | 3.6217 | 10.5 |
| 26.268 | 26.295 | 3.3900 | 8.1 |
| 28.224 | 28.217 | 3.1593 | 9.8 |
| 28.804 | 28.781 | 3.0970 | 9.9 |
| 29.199 | 29.195 | 3.0560 | 21.7 |
| 30.370 | 30.371 | 2.9408 | 10.8 |
| 31.893 | 31.909 | 2.8037 | 12.3 |
| 37.356 | 37.337 | 2.4053 | 10.3 |

SOLID STATE NUCLEAR MAGNETIC RESONANCE (NMR)
Methodology

High resolution ^{13}C spectra were obtained using high power proton decoupling and cross polarization with magic angle spinning at approximately 5 (8)kHz. The magic angle was adjusted using the ^{79}Br signal of KBr by detecting the side bands as described by Frye et. Al. (J. Mag. Res., 1992, 48, 125). Approximately 150-200mg of the sample was packed into a canistor design rotor was used for each experiment. Chemical shifts was referred op the methine carbon of an external sample of admantane taken as 37.8 ppm with reference to tetrakis trimethylsilyl silane. Table 2 shows the solid-state NMR spectrum for crystalline Form V atorvastatin.

TABLE 2. Carbon Atom Assignment and Chemical Shift for Form V

| Assignment (8kHz) | Chemical Shift |
|--------------------------------|----------------|
| Spinning Side Band | 59.64 |
| Spinning Side Band | 157.9 |
| Spinning Side Band | 161.59 |
| C12 or C25 | 183.4 |
| C12 or C25 | 177.6 |
| C16 | 166.4 |
| | 159.5 |
| Aromatic Carbons | 136.4 |
| C2-5, C13-C18, C19-24, C27-C32 | 134.4 |
| | 130.2 |
| | 128.8 |
| | 127.5 |

| | |
|-------------------|-------|
| | 122.7 |
| | 120.1 |
| | 117.0 |
| | 112.9 |
| C8, C10 | 72.3 |
| | 69.5 |
| | 67.3 |
| | 64.0 |
| Methylene Carbons | 46.5 |
| C6, C7, C9, C11 | 40.5 |
| C33 | 25.5 |
| | 24.0 |
| C34 | 20.42 |

Crystalline Form V atorvastatin of the present invention can exist in anhydrous forms as well as hydrated forms. In general, the hydrated forms are equivalent to unhydrated forms and are intended to be encompassed within the scope of the present invention.

The present invention also provides a process for the preparation of crystalline Form V atorvastatin which comprises exposing atorvastatin to a high relative humidity under conditions which yield crystalline Form V atorvastatin.

The precise conditions under which Form V of crystalline atorvastatin is formed may be empirically determined and it is only possible to give a method, which has been found to be suitable in practice.

Crystalline Form V atorvastatin may be prepared by crystallization under controlled conditions. In particular, it can be prepared either from an

aqueous solution of the corresponding basic salt such as, an alkali metal salt, for example, lithium, potassium, sodium, and the like; ammonia or an amine salt; preferably, the sodium salt by addition of a calcium salt, such as, for example, calcium acetate and the like, or by suspending heterogeneous mixture of atorvastatin in water.

In general, the use of a hydroxylic co-solvent such as, for example, a lower alcohol, for example methanol and the like, is preferred. The following non-limiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

EXAMPLE 1

Crystalline [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt
(Form V Atorvastatin)

A heterogeneous mixture of Atorvastatin Calcium (10 g) stirred in a mixture of water and absolute ethanol (140 ml: 30 ml respectively) at 40 deg centigrade for 17 hrs. The product is filtered and sucked dried. The filtered semi dried product is dried in a vacuum tray drier (650 mm Hg) for 17 hrs to get 9 g of finished product.

X-ray powder diffraction pattern (Figure 2 as shown in the accompanied drawings) demonstrates the novel crystalline nature of the product - Form V as against the heterogeneous nature of the starting material (Figure 1 as shown in the accompanied drawings)

Solid state ^{13}C nuclear magnetic resonance spectrum of Form V atorvastatin calcium (Figure 4 as shown in the accompanied drawings) was compared with that of the heterogeneous mixture of form (Figure 3 as shown in the accompanied drawings) to confirm the observations.

Example 2

Indexing of Form V Atorvastatin Calcium

The indexing of the powder diffraction pattern of the Form V atorvastatin calcium was carried using THEOR90; in the suite of
5 CRYSFIRE, a package for indexing powder x-ray diffraction pattern yielded the following results -

Total number of lines = 24

$a = 11.338(3) \text{ \AA}$; $\alpha = 83.07(7)^\circ$

$b = 11.058(4) \text{ \AA}$; $\beta = 73.47(11)^\circ$

10 $c = 17.249(11) \text{ \AA}$; $\gamma = 68.12(4)^\circ$

$V = 1923.83 \text{ \AA}^3$

We claim:

1. Crystalline Form V atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ , d-spacings, and relative intensities measured using CuK radiation:

| 2 θ -OBS | 2 θ -CALC | D-OBS | Relative Intensity(%) |
|-----------------|------------------|---------|-----------------------|
| 5.340 | 5.340 | 16.5350 | 7.9 |
| 8.618 | 8.611 | 10.2525 | 23.1 |
| 8.724 | 8.697 | 10.1282 | 25.2 |
| 8.950 | 8.946 | 9.8727 | 30.1 |
| 9.819 | 9.828 | 9.0004 | 28.7 |
| 10.094 | 10.063 | 8.7564 | 20.0 |
| 11.335 | 11.337 | 7.8004 | 21.0 |
| 16.673 | 16.671 | 5.3128 | 100.0 |
| 17.955 | 17.947 | 4.9363 | 19.3 |
| 19.161 | 19.132 | 4.6283 | 43.3 |
| 21.479 | 21.479 | 4.1338 | 69.2 |
| 22.561 | 22.568 | 3.9378 | 38.3 |
| 23.154 | 23.122 | 3.8384 | 43.2 |
| 23.576 | 23.588 | 3.7707 | 33.7 |
| 24.324 | 24.309 | 3.6563 | 6.6 |
| 24.560 | 24.559 | 3.6217 | 10.5 |
| 26.268 | 26.295 | 3.3900 | 8.1 |
| 28.224 | 28.217 | 3.1593 | 9.8 |
| 28.804 | 28.781 | 3.0970 | 9.9 |
| 29.199 | 29.195 | 3.0560 | 21.7 |

| | | | |
|--------|--------|--------|------|
| 30.370 | 30.371 | 2.9408 | 10.8 |
| 31.893 | 31.909 | 2.8037 | 12.3 |
| 37.356 | 37.337 | 2.4053 | 10.3 |

2. Crystalline Form V atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million:

5 Assignment Chemical Shift

| Assignment (8kHz) | Chemical Shift |
|--------------------------------|----------------|
| Spinning Side Band | 59.64 |
| Spinning Side Band | 157.9 |
| Spinning Side Band | 161.59 |
| C12 or C25 | 183.4 |
| C12 or C25 | 177.6 |
| C16 | 166.4 |
| | 159.5 |
| Aromatic Carbons | 136.4 |
| C2-5, C13-C18, C19-24, C27-C32 | 134.4 |
| | 130.2 |
| | 128.8 |
| | 127.5 |
| | 122.7 |
| | 120.1 |
| | 117.0 |
| | 112.9 |
| C8, C10 | 72.3 |

| | |
|-------------------|-------|
| | 69.5 |
| | 67.3 |
| | 64.0 |
| Methylene Carbons | 46.5 |
| C6, C7, C9, C11 | 40.5 |
| C33 | 25.5 |
| | 24.0 |
| C34 | 20.42 |

3. A process for the preparation of Form V crystalline atorvastatin Calcium and hydrates thereof which comprises

- (iv) stirring heterogeneous mixture of atorvastatin calcium in a mixture of water and absolute ethanol;
- (v) filtering to get the solid;
- (vi) drying to get Form V atorvastatin calcium.

4. A process of claim 3 wherein the ratio of water and absolute ethanol is in the range of 3:1 to 8:1.

5. A process of claim 4, wherein the ratio of water and alcohol is 4.67: 1.

6. A process of claim 3, wherein the stirring is carried out at 25 - 50 deg centigrade.

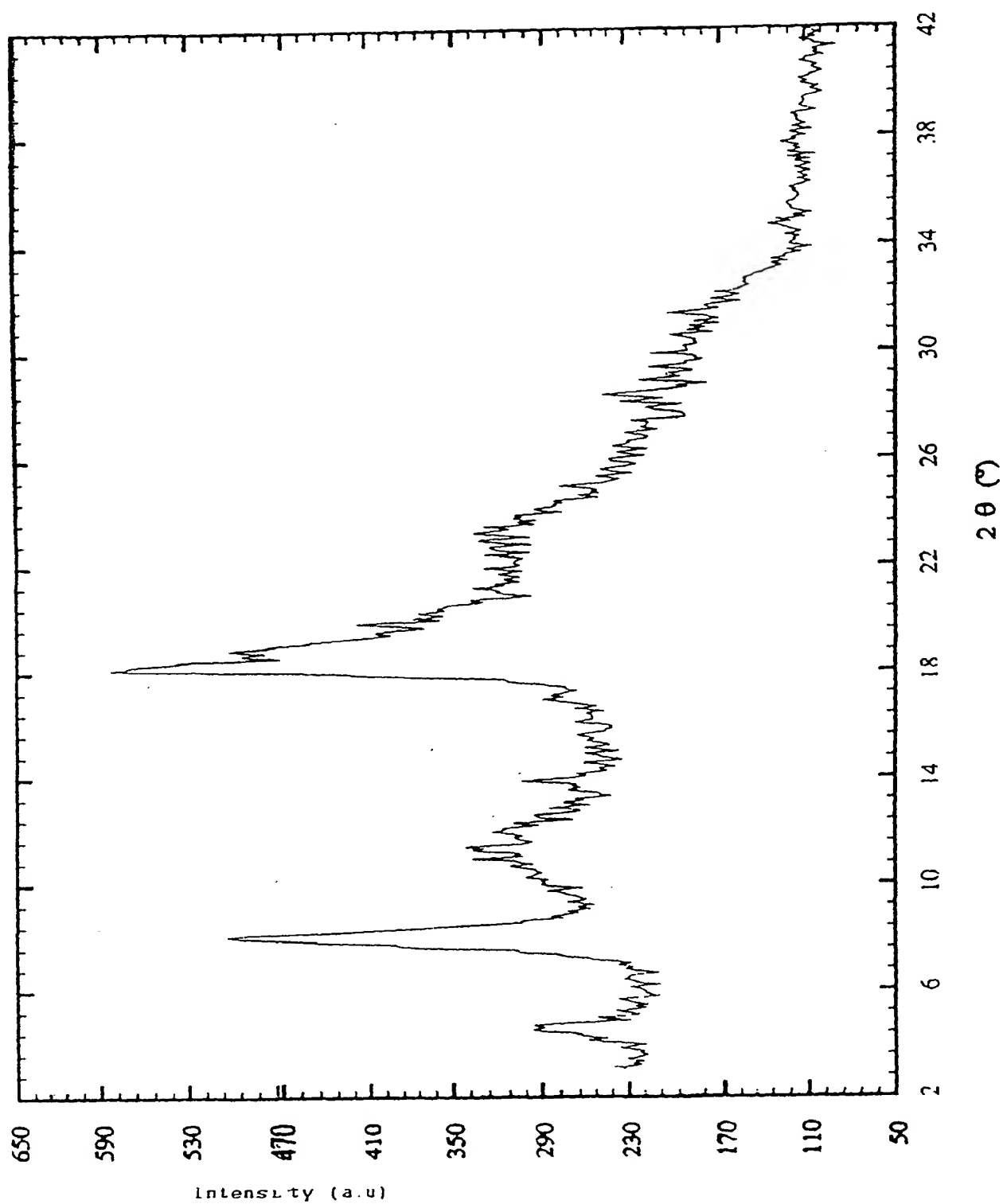
7. A process of claim 6, wherein the stirring is carried out at 40 deg centigrade.

8. A process of claim 3, wherein the stirring is carried out for 10 - 25 hrs.

9. A process of claim 8, wherein the stirring is carried out for 17 hours.

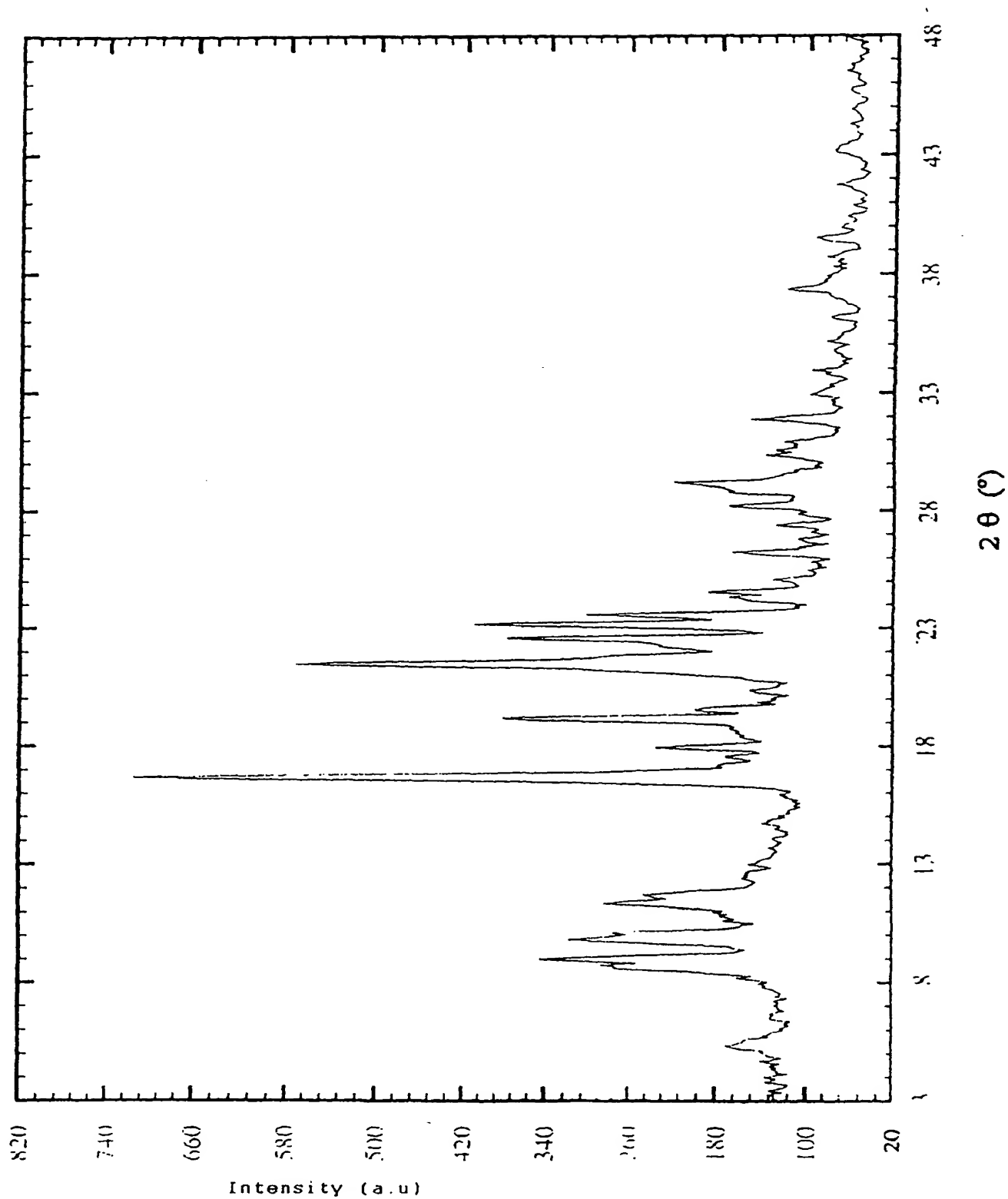
10. A process of claim 3, wherein the final product is dried in vacuum tray drier.

Figure 1



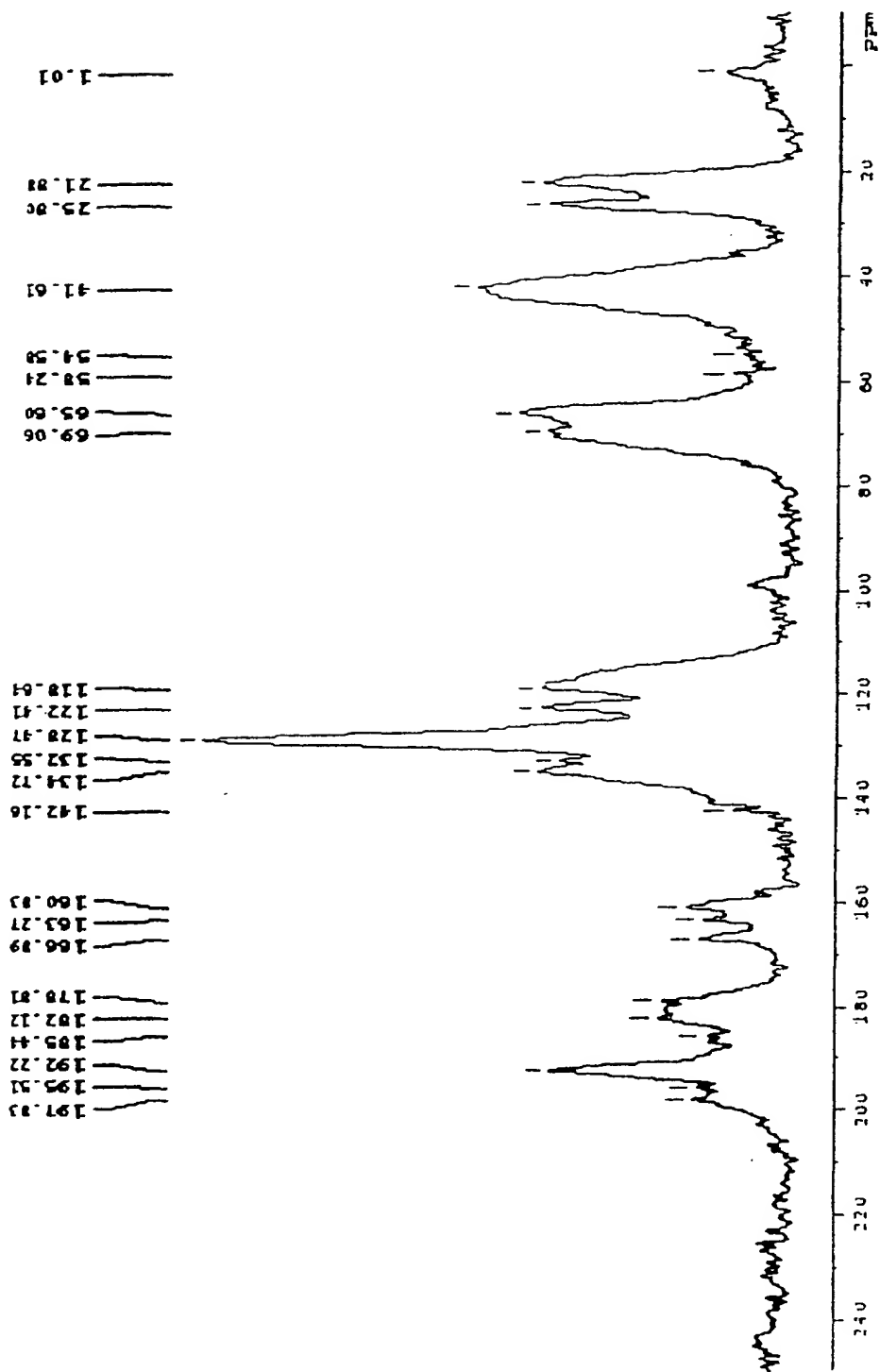
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Figure 2



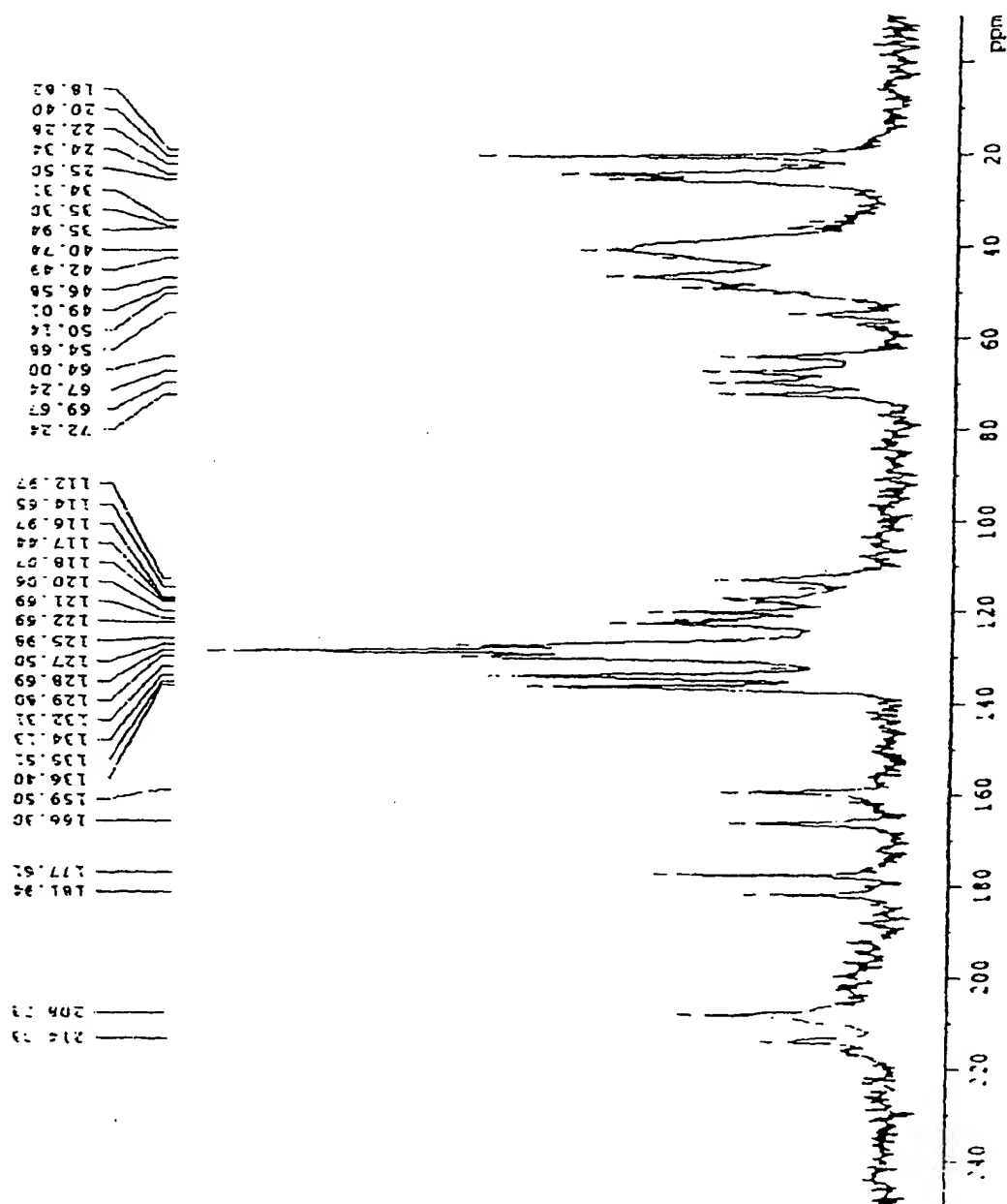
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Figure 3



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Figure 4



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INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/IN 01/00006

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D207/34 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

13 September 2001

Date of mailing of the international search report

20/09/2001

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INTERNATIONAL SEARCH REPORT

In International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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